Mediators of treatment outcome in the PACE trial of rehabilitative therapies for chronic fatigue syndrome

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Abstract

Background

Cognitive behaviour therapy (CBT) added to specialist medical care (SMC), or graded exercise therapy (GET) added to SMC, are more effective in reducing fatigue and improving physical function than both adaptive pacing therapy (APT) plus SMC and SMC alone for chronic fatigue syndrome (CFS). This paper investigates putative treatment mechanisms.

Methods

Mediation was assessed using the product of coefficients method with the 12 week measure of the mediators and the 52 week measure of the outcomes. Confounder covariates were included and treatment by mediator interaction terms were used to examine differences in mediator-outcome relationships by treatment group.

Findings

The largest mediated effect for both CBT and GET and both outcomes was through fear avoidance beliefs with an effect of larger magnitude for GET (standardised effects times 10, CBT v APT, fatigue -1·22, 95% CI = -0·52 to -1·97,physical function 1·54, CI = 0·86 to 2·31; GET v APT, fatigue -1·86, CI = -0·80 to -2·89, physical function 2·35, CI = 1·35 to 3·39). Increase in exercise tolerance (six minute walk distance) was a potent mediator of the effect of GET (v APT, fatigue -1·37, CI = -0·76 to-2·21, physical function 1·90, CI = 1·10, 2·91), but not CBT.

Interpretation

Our main finding was that fear avoidance beliefs were the strongest mediator for both CBT and GET. Changes in both beliefs and behaviour mediated the effects of both CBT and GET, but more so for GET. The results support a treatment model in which both beliefs and behaviour play a role in perpetuating fatigue and disability in CFS.

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Introduction

Chronic fatigue syndrome (CFS), otherwise known as Myalgic Encephalomyelitis (ME) is associated with profound disability (1, 2). Our recent multi-centred randomised controlled trial (RCT), PACE (adaptive **P**acing, graded **A**ctivity and **C**ognitive behaviour therapy; a randomised **E**valuation) (3, 4), compared specialist medical care (SMC) alone versus SMC with adaptive pacing therapy (APT), cognitive behaviour therapy (CBT) or graded exercise therapy (GET) for CFS.

We standardised treatments by the provision of manuals for doctors, therapists and participants (see www.pacetrial.org). At least 3 sessions of SMC were offered over 52 weeks and 14 hourly therapy sessions were offered weekly then fortnightly up to 24 weeks. A booster therapy session was given at 36 weeks. Specialist doctors gave participants general advice about managing the illness. It was suggested that extremes of activity and rest should be avoided, self-help books were suggested and specific pharmacotherapy could be offered for insomnia, pain or mood problems.

CBT involves enabling individuals to develop a consistent approach to activity. This is followed by gradual increases in activity. CBT also encourages people to develop healthy sleep patterns and enables them to identify and challenge unhelpful cognitions (5) with the primary aims of reducing fatigue and improving physical function. It is based on a theoretical model which supposes that unhelpful interpretations of symptoms, fearful beliefs about engaging in activity, and excessive focus on symptoms are central in driving disability and symptom severity (5). These cognitive responses are associated with unhelpful behavioural

patterns, including avoidance of activity together with excessive rest, and all-or-nothing behaviour – a pattern of pushing too hard or being over-active when feeling well.

GET for CFS involves establishing a baseline of consistent activity and regular sleep-wake cycle, then encouraging mutually negotiated increments in the time spent physically active (most commonly walking) followed by an incremental increase in the *intensity* of exercise to a target of half an hour of physical exercise five times a week. It is based on a model of both de-conditioning (loss of muscle strength and reduced exercise capacity) and avoidance of activity (6). Both these factors are thought to maintain fatigue and disability (7-9). Systematic reviews have suggested that patients with CFS are less physically active and have less isometric muscle strength and reduced exercise capacity than healthy controls (10, 11).

CBT and GET in the context of this trial had much in common, but could be differentiated. Both involved agreeing an achievable and consistent baseline of activity and then increasing activity, although GET specifically focused on physical exercise. CBT addressed unhelpful thoughts but GET did not. CBT and GET were clearly distinguished by independent raters who rated treatment integrity and were blind to treatment arm (3).

APT for CFS involved encouraging participants to plan activity with a view to avoiding increases in symptoms, and limiting demands and stress. It included specific advice not to undertake activities that demanded more than 70% of participants' perceived energy envelopes in order to establish a baseline of achievable activity, and then increasing as able (3). It was based on the envelope theory of chronic fatigue syndrome in which the illness is assumed to be entirely physical, with fixed energy levels (12).

We found that, when added to SMC, CBT and GET had greater success in reducing fatigue and physical disability than APT or SMC alone (3). The number of therapy sessions received was similar across groups. However the SMC alone group received a median of two more SMC sessions than the therapy supplemented treatment groups. Anti-depressant and hypnotic use did not differ significantly between groups, either at baseline or at follow-up. The interval between pre-treatment and follow up was the same. There were no important differences in safety outcomes between treatment options. Mean differences between groups on primary outcomes almost always exceeded predefined clinically useful differences for CBT and GET when compared with APT and SMC. In all comparisons of the proportions of participants who had either improved or were within normal ranges for these outcomes, CBT and GET were superior to APT or SMC alone (3). Improvements were moderate in size and therefore outcomes need to be improved further. Identifying mechanisms of change may elucidate ways in which effective treatments can be further developed, improved, or optimised. The study of mediation may also provide information about the utility of the model on which treatment is based.

A couple of studies have examined potential treatment mechanisms in relation to GET. The first RCT of GET for CFS found that those who rated themselves as better were no fitter or stronger than the rest (13), but that better exercise tolerance was associated with being fitter (lower heart rate response to sub-maximal exercise) (8). A second trial of GET also suggested that physical reconditioning was not a mediator of the effect of treatment, but that a reduction in symptom focusing and increased exercise tolerance (as assessed by maximal heart rate achieved with exercise) mediated change in mental and physical fatigue (9).

There have been several studies of treatment mechanisms of CBT. Although a formal mediation analysis was not carried out, a reduction in fearful cognitions was associated with better outcomes in a trial of CBT compared to relaxation (14). More recently, Wiborg and colleagues found that a decrease in focusing on fatigue mediated the effect of CBT in one trial (15), while, in another trial, the effect of therapy was mediated by a decrease in perceived problems with activity and an increase in the sense of control over fatigue (16). These and other similar studies have relied on cross-sectional data (6, 8, 9, 14-17). Consequently, a temporal separation between the mediator and outcomes was missing, making it difficult to ascertain the direction of the causal relationship.

The recent Fatigue Intervention by Nurses Evaluation (FINE) trial compared pragmatic rehabilitation to supportive listening or treatment as usual in CFS. Pragmatic rehabilitation contained elements of CBT and GET. It involved regular sessions with a health professional, and included physiological explanations for symptoms with graded activity but also ensured the individual had appropriate rest and relaxation. It was delivered at home, over an 18-week period by specially trained general nurses. A longitudinal mediation analysis found that reducing both catastrophising and avoidance of activity, measured immediately after the end of treatment, at 20 weeks, mediated a reduction in fatigue at 70 weeks follow up (18).

We designed the PACE trial with an aim of gaining perspective on the mechanisms of change through the identification of mediators. To this end, the trial measured a range of putative mediators and outcomes. Our aims were:

1) To explore whether specific putative mediators measured at 0, 12, 24 and 52 weeks changed to a different extent between treatment groups.

2) To examine whether these factors mediated differences in fatigue and physical function in CBT and GET compared to APT and SMC.

Based on models of CFS and previous findings we hypothesized that fearful beliefs, in particular fear avoidance beliefs (e.g. 'I am afraid that I will make my symptoms worse if I exercise'), symptom focusing (e.g. 'I think a great deal about my symptoms'), catastrophising (e.g. 'I will never feel right again'), and avoidance behaviour (e.g. 'I stay in bed to control my symptoms') would mediate change in fatigue and physical function in both CBT and GET. We also hypothesised that timed walking distance as a measure of exercise tolerance, but also as a more objective measure of activity engagement, would mediate change in both outcomes for CBT and GET. Based on the fact that embarrassment avoidance, damage beliefs, self-efficacy, perception of effort and unhelpful sleep routines are targeted in CBT these additional processes were also examined. Some empirical evidence exists to support their inclusion. Embarrassment avoidance (e.g. 'I am embarrassed about my symptoms') and damage beliefs (e.g. 'Symptoms are a signal that I am damaging myself') have been shown to change with routine CBT and an exploratory latent trait model suggested that the observed partial mediation model generalized to illness-related cognitive traits (19). There is evidence that self-efficacy may be an important transdiagnostic mechanism of change (20, 21). Perception of effort with exercise is increased in people with CFS and we believed it was likely to change with rehabilitative treatments such as CBT and GET (13). A poor sleep routine is commonplace in people with CFS (22), and establishing a sleep routine is a focus of CBT and therefore may improve fatigue and disability. Finally on the basis of previous trials we predicted that anxiety, depression, all or nothing behaviour and fitness would not mediate treatment outcome either in CBT or GET.

Methods

Design

641 participants were recruited from consecutive new outpatients attending six specialist CFS clinics in the UK National Health Service. Participants fulfilled the Oxford criteria for CFS (2), which requires fatigue to be the principal symptom. All participants were medically assessed by the specialist clinic doctors to exclude alternative diagnoses (4). The West Midlands Multicentre Research Ethics Committee (MREC 02/7/89) approved the original PACE study.

The main results of the trial have been reported elsewhere; 88% received an adequate dose of treatment and only 2% were completely lost to follow-up (3). We conducted a planned secondary mediation analysis of the PACE trial comparing SMC alone or SMC plus APT to SMC plus CBT and SMC plus GET for patients with chronic fatigue syndrome (3, 4).

Description of the generic mediation model

Mediation is a hypothesized causal chain in which a baseline variable R affects a post baseline mediating variable M, which in turn affects an outcome variable Y (23). In the case of a trial such as PACE, R is treatment group, for example CBT compared to APT, and an example mediator and outcome might be fear avoidance and physical function, as shown in Figure 1. If the intervening variable M explains the relationship between R and Y (the relationship between R and Y is no longer statistically significant when adjusting for M in the model and the estimate for R is essentially equal to zero), then M is a mediator and we have a *full* mediational model (24, 25). If the intervening variable only partially explains the relationship between R and Y (the M effect is statistically significant but R is not equal to

zero and/or still has a significant effect on Y after including M in the model) the model is consistent with *partial* but not *full* mediation (24, 25).

Measures

The measures, which are described in more detail in the web appendix, were all assessed at 0, 12, 24 and 52 weeks after randomisation (except for the walk test, which was not done at 12 weeks due to the anticipated burden for participants) and these were described using unadjusted mean profile plots. For the mediation analysis the 52 week measure of the outcome and the 12 week measure of the putative mediator were used. The 12 week measure of the mediator was used in order to capture change as early as possible and have the maximum possible separation between mediator and outcome measurements. This temporal separation between the variables was employed to meet the implicit mediation model assumption of ordering of the variables in the causal chain (23). Respecting this ordering is important for rendering causal mediation inferences more plausible. The exception was the walk test where the 24 week measure was used.

The primary outcomes were fatigue measured by the Chalder fatigue scale and physical function measured by the physical function subscale of the SF-36. Several of the putative mediators were measured using the Cognitive Behavioural Responses Questionnaire (CBRQ); these were five cognitive measures: catastrophising, fear avoidance beliefs, damage beliefs, symptom focusing, and embarrassment avoidance beliefs, as well as two behavioural measures: all-or-nothing behaviour and avoidance/resting behaviour. Other putative mediators were: self-efficacy, sleep measured using the Jenkins Sleep Scale, anxiety and depression measured using the Hospital Anxiety and Depression Scale, fitness and perceived

exertion measured using a step test, and walking distance measured using the six-minute walk test.

Statistical analysis

The analyses were carried out using Stata, Version 10. The main outcomes were prorated only when there were at most two items missing from the scale. The mean value of complete item scores was calculated and used in place of missing scale values. The mediators were not prorated since most with missing data were missing all items. The main analyses, including regression models, were limited to participants with complete records for all variables considered. Mediators were summarised using the mean, standard deviation and 95% confidence interval for the mean.

Mediation was assessed from regressions using the product of coefficients method (POC) (23), shown in both equation (below) and path diagram form (Figure 1), where Y is the outcome, M is the mediator, R is randomised treatment group and ε is an error term (other covariates are not shown for simplicity):

$$Y_i = \alpha_1 + \beta_1 R_i + \varepsilon_{i1} \quad \text{(Model 1)}$$
$$M_i = \alpha_2 + \beta_2 R_i + \varepsilon_{i2} \quad \text{(Model 2)}$$
$$Y_i = \alpha_3 + \beta_3 R_i + \gamma M_i + \varepsilon_{i3} \quad \text{(Model 3)}$$

The β_1 parameter is the overall effect of the treatment on the outcome, referred to as the *c* pathway in the mediation literature. The mediated (indirect) effect is then β_2 multiplied by γ, or *a* multiplied by *b* from Figure 1. The direct effect of R on Y in the presence of M is given by β_3 and is called the *c'* pathway. In addition to the temporal ordering assumption mentioned in the Measures section, the usual assumptions are associated with the regressions used in the

POC method, including: accurate measurement, linearity, normally distributed residuals and no omitted variables (23). The latter assumption has received a great deal of attention recently in mediation, in particular in clinical trials where despite randomisation, there could still be confounding of the non-randomised relationship between the mediator and outcome (U in Figure 1) (23, 25, 26). If there are unmeasured variables that influence both mediator and outcome, the estimate obtained for this relationship may be biased. While unmeasured confounding cannot be ruled out, adding baseline variables that may be confounders makes a causal interpretation more plausible; further covariates were included in the models to address this (23, 26). For example, if these variables were confounders, including them will have provided an adjusted and hopefully more accurate estimate, and if they were proxies for unmeasured confounders they may have partially adjusted for the omitted variables as well. The variables were selected for inclusion in models because they were thought to be potential predictors of mediators and outcomes. Age and gender could also be proxies for other variables that were not measured. The original trial stratification factors were included in order to respect the trial design. The baseline variables were: centre, Standardised Clinical Interview for DSM-IV (SCID) depression status (27), London criteria for myalgic encephalomyelitis (ME) status (28), International criteria for CFS status (1), baseline measure of mediator, baseline measures of both outcomes, baseline work and social adjustment scale (29), any anxiety disorder as determined using the SCID, age, gender, CFS patient group membership, receipt of financial benefits, being in dispute regarding financial benefits, physical illness attribution, fibromyalgia status (30), illness duration, Jenkins sleep score, employment status, body mass index, and physical symptoms (Patient Health Questionnaire-15) score (31). All of these variables were included in all models. Medication use variables were available, but were not used. This was because these were not theorised to be likely confounders in the context of the large number of other confounders included.

The POC method shares some aspects with two other methods commonly applied to the study of mediation, the Baron-Judd-Kenny causal steps approach and the use of the structural equation model framework (23-25). The causal steps approach requires the overall treatment effect, or the effect of β_1 in Model 1, to be significant before proceeding. Like others (23, 26) we do not believe this to be necessary. Rather, we suggest examining whether there is an absence of a treatment effect on the mediator, an absence of a mediator effect on the outcome, or the occurrence of opposing direct and indirect effects. The structural equation modelling framework requires some additional assumptions such as multivariate normality.

The mediator models (Model 2) had the 12 week post-randomisation measurement of each of the putative mediators as the dependent variable (except for six minute walking distance where the 24 week measure was used) and both treatment arm and the potential confounders as covariates. The outcome models had the 52 week post-randomisation measure of each of the outcomes as the dependent variable, with treatment arm, the 12 week measure of the putative mediator and the potential confounders as covariates (Model 3). Tests of interaction between treatment and mediator on outcome were all non-significant, allowing a coefficient *b* to be estimated that was common to all treatments (see Figure 1), improving efficiency and model stability. The statistical significance and magnitude of the model parameters associated with the *c* and *c'* pathways were used to assess whether mediation was partial or full.

All continuous variables were standardised (each value had the mean of the variable subtracted and was divided by the standard deviation of the variable) so that parameters represented changes in standard deviation (SD) units. Results from the mediator models are therefore in SD units of the mediator; results from the outcome models are in SD units of the outcome. The *a* multiplied by *b* mediation effect here therefore constituted the recommended

standardised mediation effect in SD units of the outcome (23), with a bias-corrected bootstrap 95% confidence interval. This allowed for asymmetry of the interval, obtained using bootstrapping with a thousand repetitions (23, 32). Bootstrap confidence intervals can have incorrect endpoints; the bias-corrected bootstrap adjusts the interval endpoints by a constant reflecting the approximate median bias of the bootstrap estimate in units of the standard normal distribution (32). All mediated effects were multiplied by 10 to decrease the number of decimal places in figures and tables for visualisation purposes. Mediated effects have also been expressed as the proportion of the overall effect of the treatment on the outcome, in other words (ab/c)*100. Note that the % mediated would not be expected to add up to 100% within a given comparison as the mediators have been studied individually and any overlapping effects have not yet been examined. Both CBT and GET were compared with APT and SMC separately. Some mediated effects have been compared between CBT and GET using Wald tests of the equality of the two parameter estimates in the mediator models (Model 2).

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Results

Information on data completeness (Table A), balance of baseline variables between the treatment groups (Table B) in the mediation analysis data subset, and differences between the people with and without complete data for the mediation analysis (Table C) are available in

the web appendix. Unadjusted mean profile plots of the outcomes over time are also available in the Web appendix (Figure A).

Pattern of change over time in variables used as mediators at 12 weeks

Plots and summary statistics for the putative mediators (Figure 2 and Web appendix Table D) show similar patterns to those of the outcomes with greater improvement with CBT and GET, the majority of change occurring during the treatment phase. There was little change between the end of treatment at 24 weeks and follow up at 52 weeks. There were some exceptions to the general pattern; all or nothing behaviour decreased to a similar level for APT, CBT and GET, and fear avoidance improved more in the GET group than for CBT.

Relationships between treatments and mediators

Figure 3 shows the treatment effects of CBT and GET, as compared to APT and SMC, on the putative mediating variables. These effects equate to the *a* path shown in Figure 1 and are differences in mediator SD units between compared treatments. Compared to APT and SMC, both CBT and GET significantly decreased catastrophising, avoidance behaviour, fear avoidance beliefs and damage beliefs. The strongest effects were on fear avoidance beliefs (CBT v APT -0·64, 95%CI -0·46 to -0·83, GET v APT -0·98, 95% CI -0·80 to -1·16) and damage beliefs (CBT v APT -0·61, 95% CI -0·43 to -0·78, GET v APT -0·56, 95% CI -0·39 to -0·73). GET had a larger effect on fear avoidance beliefs than did CBT ($p < 0.001$). Compared to APT, both CBT and GET decreased symptom focusing, and compared to SMC, the treatments significantly decreased all or nothing behaviour, sleep problems and increased self-efficacy. In addition, CBT also decreased symptom focusing, embarrassment avoidance and HADS depression as compared to SMC. In both types of comparisons, GET significantly

increased the number of metres walked while CBT did not (GET v APT 0·43, 95% CI 0·25 to 0·61, GET v SMC 0·46, 95% CI 0·28 to 0·63, p for CBT versus GET = 0.001). There were no effects on HADS anxiety, physical fitness or the adjusted perception of effort measure (Borg scale).

Relationships between mediators and outcomes

Figure 4 shows the relationships between the putative mediators and the outcomes. These effects equate to the *b* path shown in Figure 1, and are differences in outcome SD units for a 1 SD unit change in the mediator. The models show that increases in catastrophising, all or nothing behaviour, embarrassment avoidance, fear avoidance beliefs, damage beliefs, HADS depression, sleep problems and Borg scores (=worsening) were associated with significantly worse fatigue, which means that when treatments reduced these variables, there was a reduction in fatigue. Increases in (= better) scores of self-efficacy and metres walked were associated with significant decreases in fatigue. The strongest effects on fatigue were for metres walked and embarrassment avoidance (-0·32, 95% CI -0·20 to -0·44 and 0·27, 95% CI 0·16 to 0·38). All of the mediators with the exception of the physical fitness measure were associated with physical function, and similar to fatigue, these were in the directions expected. The largest effects here were for metres walked and HADS depression (0·44, 95% CI 0·34 to 0·55 and -0·33, 95% CI -0·23 to -0·43). Self-efficacy also had reasonably strong effects on both outcomes.

Mediation effects in PACE adjusting for potential confounders

Figures 5 and 6 show standardised mediation effects (times 10) for all mediators and treatment comparisons studied (parameter estimates and confidence intervals and proportion mediated shown in Web appendix, Table E). Fear avoidance beliefs had the largest mediated effect on both fatigue and physical function for both CBT and GET (fatigue CBT v APT -1·22, 95% CI -0·52 to -1·97, GET v APT -1·86, 95% CI -0·80 to -2·89, physical function CBT v APT 1·54, 95% CI 0·86 to 2·31, GET v APT 2·35, 95% CI 1·35 to 3·39). This accounted for 51% of the overall effect on physical function for GET and 37% for CBT, as compared to APT. The proportions were 61% and 34% for the same comparisons for the fatigue outcome. Damage beliefs also mediated the effects of both treatments on both outcomes – the effects were the second largest in magnitude of the cognitive mediators for comparisons with APT (fatigue CBT v APT -0·85, 95% CI -0·23 to -1·68, GET v APT -0·78, 95% CI -0·24 to -1·58, physical function CBT v APT 1·26, 95% CI 0·61 to 2·13, GET v APT 1·16, 95% CI 0·57 to 2·02), with approximately 25 – 30 % of the overall effect on both outcomes being accounted for by damage beliefs. Damage beliefs and self-efficacy were mediators of similar magnitude for the SMC comparisons. For comparisons with APT, self-efficacy was either a relatively weak or non-significant mediator because it didn't change significantly more with either CBT or GET than with APT (Figure 3). Catastrophising and avoidance behaviour were also significant mediators of treatments for all comparisons and both outcomes, albeit with effects of smaller magnitude as compared to fear avoidance (Figures 5 and 6 and Web appendix Table E). For example, the largest proportion of the overall effect explained for catastrophising was 18% for CBT versus APT for the physical function outcome. The number of metres walked (exercise tolerance) was a strong mediator of the effect of GET on both outcomes, both for comparisons to APT and SMC (fatigue GET

v APT -1·37, 95% CI -0·76 to -2·21, GET v SMC -1·46, 95% CI -0·75 to -2·34, physical function GET v APT 1·90, 95% CI 1·10 to 2·91, GET vSMC 2·03, 95% CI 1·16 to 2·99), with this accounting for approximately 33% of the overall effect for the comparisons to APT. Other mediated effects which were statistically significant for both outcomes were embarrassment avoidance for CBT for both comparisons, all or nothing behaviour and sleep problems for CBT and GET comparisons to SMC and depression for CBT versus SMC only. One mediating effect was limited to the outcome of physical function: symptom focusing was a mediator of CBT as compared to both APT and SMC. Figure 7 shows example path diagrams for the fear avoidance beliefs mediator. Fear avoidance was a partial rather than a full mediator in both cases. This can be seen by looking at the *c'* path, or residual direct effect of treatment. This path was only non-significant for the GET v APT comparison for the physical function outcome, and even so it still differs substantially from zero.

The analysis was repeated using the full information maximum-likelihood structural equation modelling framework that required the weaker assumption of data missing at random and allowed for loss selective on covariates and measured outcomes as described in the Methods (35). The effective sample sizes were increased to: 613 to 617 for questionnaire measures (up to 96% complete), 534 for fitness (83% complete), 535 for perceived exertion (Borg, 84% complete) and 595 for walking (93% complete). Results remained essentially unchanged, though some effects that were not significant but borderline in the original analysis became significant: walking for CBT versus SMC, symptom focusing for GET versus APT and physical function and depression for GET versus SMC for fatigue.

Discussion

Our main finding was that fear avoidance beliefs were the strongest mediator for both CBT and GET. Fear avoidance beliefs are characterised by fears that activity or exercise will make symptoms worse. Damage beliefs were also important in comparison with APT. Exercise tolerance as measured by the number of metres walked in a fixed time was a strong mediator of GET alone. Other cognitive and behavioural measures, such as catastrophising and avoidance behaviour, had small but significant mediation effects for both of the effective treatments affecting both outcomes.

The results suggest that GET may be more specific in its effects than CBT, with two strong mediators, fear avoidance beliefs and timed walking distance. The increase in exercise tolerance (walking distance) without an increase in exercise capacity (fitness) may have been facilitated by the mediating effect of reduced fear avoidance beliefs. This is in keeping with the findings of increased exercise tolerance in a previous trial (9).

For CBT, several mediators were implicated with smaller effects of similar magnitude, including depression for comparisons to SMC. Although we are cautious about over interpreting the role of depression as a mediator, CBT is an evidence based approach for depression which comprises a variety of different procedures including behavioural activation and cognitive restructuring not dissimilar to CBT for CFS.

Fear avoidance beliefs, the strongest mediator, accounted for up to 60% of the overall effect, providing evidence for partial mediation. Many of the mediators accounted for much smaller proportions of the overall effects. This suggests that in some cases the effects of treatment on

outcomes may have been mediated through several small effects and that some of the overall treatment effects were mediated through variables that were not measured.

These findings, which benefit from temporal separation in mediator and outcome measures, support the preliminary findings of previous studies in CFS (14, 18). Deale et al (1998) found avoidance behaviour was a mediator of the effect of CBT on physical function cross-sectionally (14). Recently, the mediation analysis of the FINE trial of pragmatic rehabilitation found that embarrassment avoidance, all or nothing and avoidance behaviour were cross-sectional mediators of the treatment effect (18), whereas catastrophising and avoidance behaviour were prospective mediators of the effect on fatigue.

Symptom focusing was found to be a cross-sectional mediator of CBT and GET on fatigue in two previous studies (9, 15), was not a mediator of the effect of the pragmatic rehabilitation treatment in the FINE trial (18) and only a weak mediator of the effect of CBT on physical function in our study. These dissimilar results could be explained by differences in the measurement of symptom focusing, due to the fact that the mediators were assessed in a cross-sectional fashion in the previous studies, or due to differences in treatment protocols.

Wiborg and colleagues found perception of activity and an increase in sense of control were mediators of the effect of CBT on fatigue, which is similar to our findings (16). Fitness and perception of exertion did not appear to mediate the effect of CBT or GET here, a finding consistent with previous studies (8, 9, 18). Our study is the first to assess differences in timed walking distance. This was found to mediate the effect of GET, suggesting that increasing tolerance of physical activity may produce benefit without improving physical fitness. However, it must be acknowledged that the walking test might not reflect activity or exercise

levels in everyday life and may provide an explanation for why Wiborg et al (2010) found no evidence that actometer-measured physical activity mediated the effect of CBT (17).

This mediational analysis strengthens the validity of our theoretical model of CBT and supports the idea that a similar model is valid for GET by confirming the role of fearful beliefs and avoidance behaviour. The review of beliefs in CFS and fibromyalgia (33), suggested that fear and avoidance of movement were related to poorer outcomes. This fits with findings from a previous study which showed that fear avoidance beliefs partially mediated the relationship between avoidance behaviour and treatment outcomes at six months following CBT (19). The results in the current paper support these findings suggesting that fearful beliefs can be changed by directly challenging such beliefs (as in CBT) or by simple behaviour change with a graded approach to the avoided activity (as in GET).

Clinically, the results suggest that therapists delivering CBT could encourage more physical activities such as walking. This may enhance the effect of CBT and may be more acceptable to patients. Previous feedback from young people with CFS suggested that they liked the behavioural aspects of CBT, but did not like cognitive restructuring (34).

The strengths of this study are that the results originate from the largest trial of CBT and GET to date. The study had few drop-outs and adherence to treatment was high. The study of mediation was incorporated at the design stage of PACE, so mediators were measured at mid-treatment allowing the study of mediator measurements taken prior to those of the outcomes. Temporal ordering of variables and the inclusion of many potential confounding variables makes causal inferences about the mediated effects more plausible. Both self-report and

objective measures were used, and both were found to mediate treatment effects, lending credence to the results.

Limitations include the issue of potential residual unmeasured confounding of the mediator to outcome path. However, given that adjustment was made for several potential confounders it seems unlikely that residual confounding could explain the mediation effects found, especially for the stronger effects. It is possible that variables were measured with error; however, this generally leads to the dampening of effects and so would have disguised a variable's mediating effect rather than leading to a variable being found to be a mediator in error. This was a complete case analysis, requiring an assumption of missing completely at random, which was a greater concern for the step and walk-test mediators, where more data was missing, than for the questionnaire-based mediators. However, the results of the full information maximum-likelihood analysis did not differ greatly from the complete case analysis, suggesting serious missing data biases were unlikely.

In an ideal world mediators would have been assessed at every session. Given the pattern of change in the mediators was similar to the pattern of change in the outcomes it is possible that the variables were influencing each other reciprocally and more measures might have helped clarify this. However, this was prohibitive in this trial due to cost and possible measurement fatigue on the patients' part. Results from longitudinal analyses incorporating all available mediator and outcome measurements will be discussed in future publications. In addition, we were only able to assess walking at 24 weeks when most of the change in outcomes had occurred. It would have been more convincing as a mediator if it had been assessed at 12 weeks mid treatment. We didn't find evidence of differing *b* paths (relationships between the mediators and outcomes) by treatment group, but we may have

had limited power to test for these interactions. Given the number of mediators that have been considered it is possible that some of the findings could be due to chance, in other words, type 1 errors may have been made. This should be kept in mind in interpreting the findings, in particular for the more exploratory mediators. Finally, in this paper we focused on single mediators and the effects of some of these variables are not likely to be independent. Our forthcoming analysis of multiple mediator effects will provide more information on this issue.

Conclusions

CBT and GET treatments appear to work mainly through common mechanisms, changing fear avoidance beliefs. CBT and GET do not work by improving fitness or by decreasing perception of effort, nor do they work by reducing anxiety. However, GET increased exercise tolerance, as compared to APT or SMC, indicating that a change in behaviour in the absence of a direct focus on changing beliefs can improve both fatigue and physical function. Mediation of the treatment effect was partial which means that part of the treatment response remains unexplained. Multiple mediator analysis will provide more information about the degree to which the different mediators exert independent effects. These findings are clinically relevant. They provide evidence for the mechanisms of change in treatment and demonstrate that CBT and GET work primarily in similar ways i.e. by changing fear avoidance beliefs. Future studies should focus on improving self-efficacy and increasing physical activity as these identified mediators had strong relationships with the outcomes. This may lead to greater improvements in outcomes.

Panel 1: Research in context

Systematic review

For the adaptive **P**acing, graded **A**ctivity and **C**ognitive behaviour therapy; a randomised **E**valuation (PACE) trial, PubMed and Cochrane Library databases were searched up to November 6, 2010, and the detailed findings of this are in the Research in Context box in the primary trial publication (3). This review concluded that cognitive behaviour therapy (CBT) and graded exercise therapy (GET) were moderately effective treatments for chronic fatigue syndrome (CFS), and the results of the PACE trial agreed with this (3). There have been few papers published on mediation of treatment effects in CFS, so these were found through pre-existing knowledge of publications, reference lists in these publications and in the course of routine searches for publications in the field using PubMed up to May 28, 2014. There is an early paper formulating a general model for fatigue in a group of patients with CFS (6). There are also several studies using cross-sectional mediator and outcome data to study either mediation or relationships between mediators and outcomes for CBT (14-17) and for GET (9, 13). The recent mediation analysis of the FINE trial of pragmatic rehabilitation for CFS used longitudinal data to study mediation (18). In cross-sectional studies, both CBT and GET were found to target cognitive measures such as fear of, and perceived problems with, activity, symptom focusing, and self-efficacy (9, 14-16). Fitness measures did not mediate the effects of the treatments (9, 17). The FINE trial showed both cognitive (catastrophising) and behavioural (avoidance behaviour) variables to be longitudinal mediators of the relationship between pragmatic rehabilitation and fatigue (18).

Interpretation

Given that the PACE trial showed moderate effects of CBT and GET treatments, it was of interest to understand through which variables these overall effects were mediated. We confirm that fear avoidance beliefs partially mediate the effects of CBT and GET on physical function and fatigue outcomes, and that fitness measures do not appear to mediate the effects of either treatment. We have also shown that changes in behaviour, i.e. increased walking distance and reduced avoidance behaviour, can also transmit the effects of treatments to the outcomes, in particular walking distance for GET. We did not find much evidence for symptom focusing as a mediator in this study. These findings from longitudinal data respecting the hypothesised causal ordering of mediators and outcomes are likely more robust than those from past studies using cross-sectional data. In addition, we identified mediators with strong relationships with outcomes, self-efficacy and walking distance; if treatments for CFS could be refined to target these mediators to a greater extent they may effect greater improvements in outcomes.

Author contributions

The PACE trial co-principal investigators were PW, TC and MS. TC conceived of and designed the clinical aspect of this study of mediation with contributions from PW and MS. KG designed and completed the statistical analysis. The manuscript was written by TC, KG, PW and MS. AP consulted on the statistical analysis and interpretation of the results.

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Conflicts of interest

PDW has done voluntary and paid consultancy work for the United Kingdom government and a reinsurance company. TC has received royalties from Sheldon Press and Constable and Robinson. MS has done voluntary and paid consultancy work for the United Kingdom government, has done consultancy work for an insurance company, and has received royalties from Oxford University Press. KG and AP have no conflicts of interest to declare.

Disclaimer

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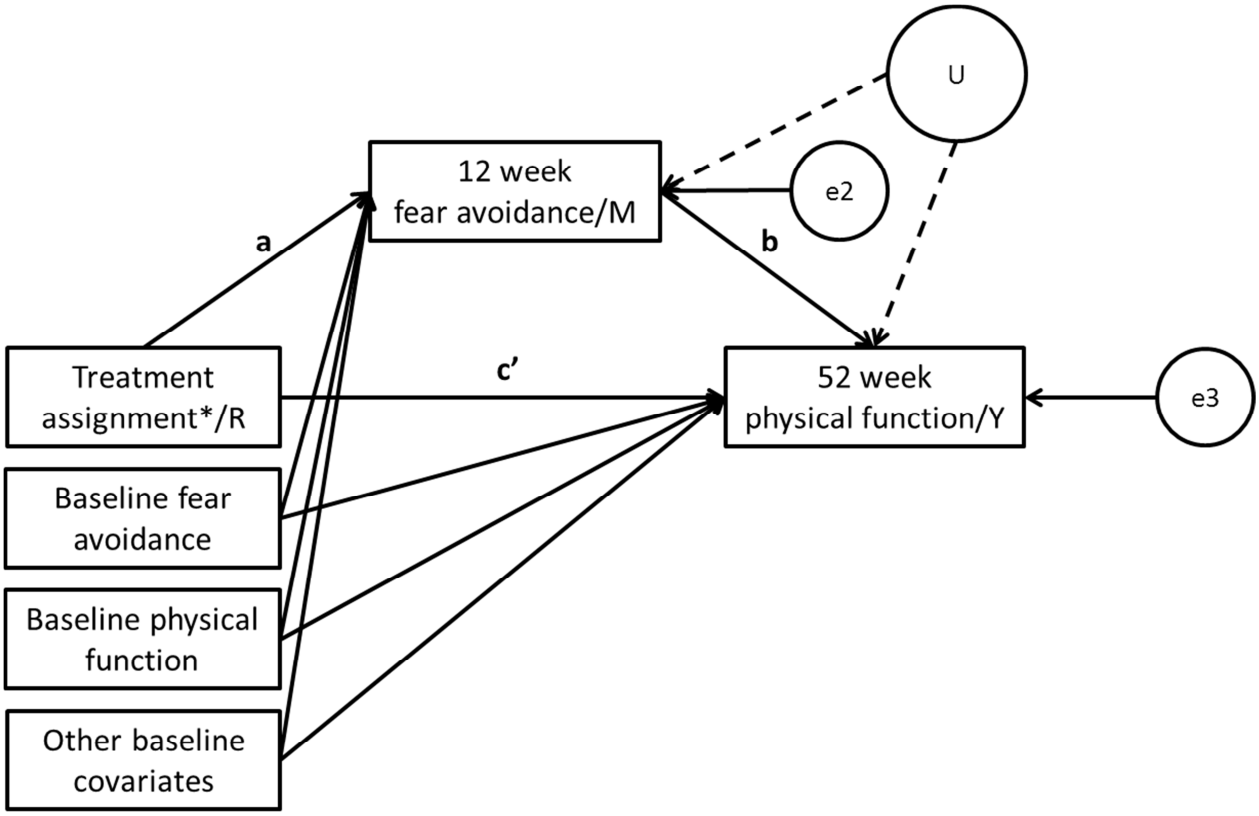
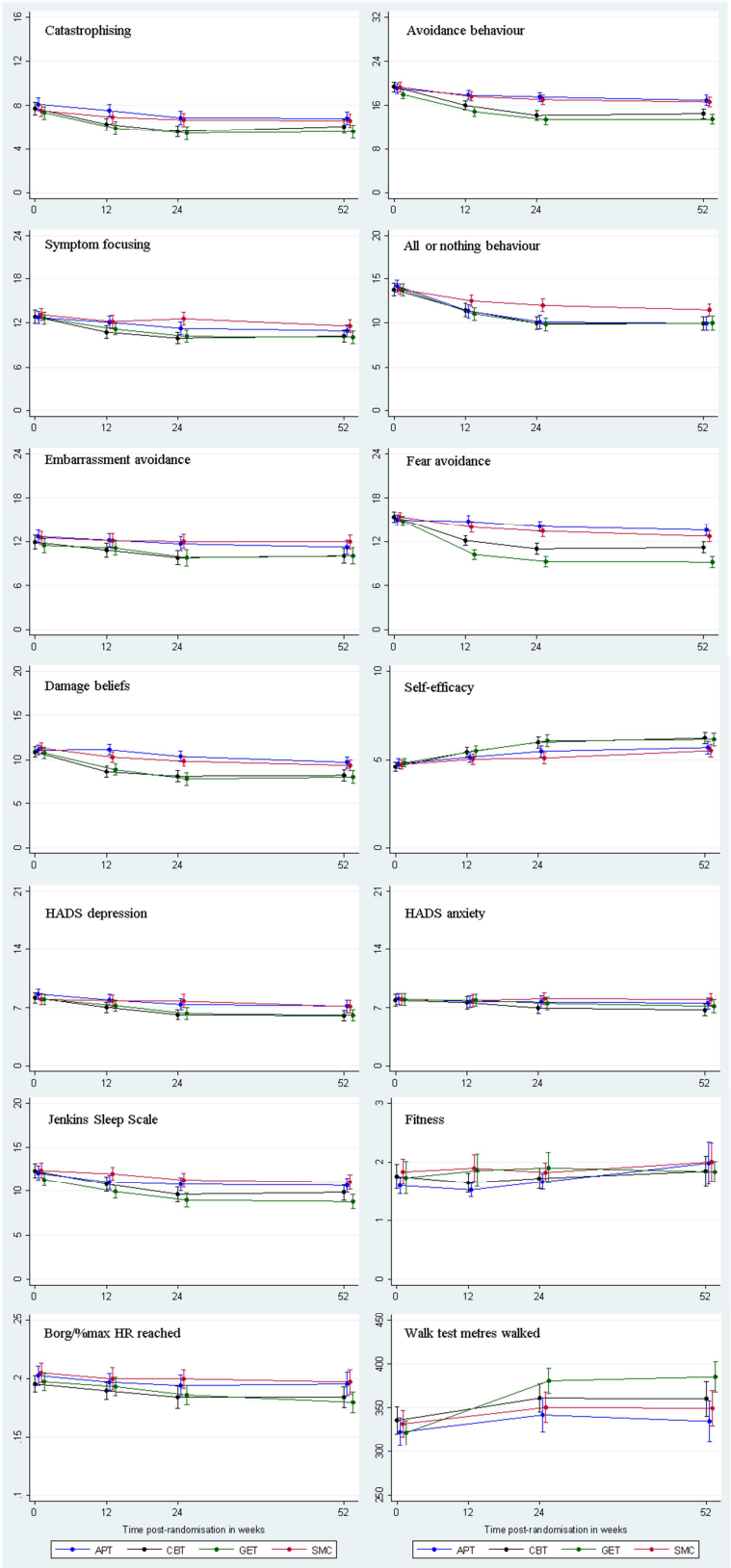
Figures

Figure 1. Example of a PACE mediation model



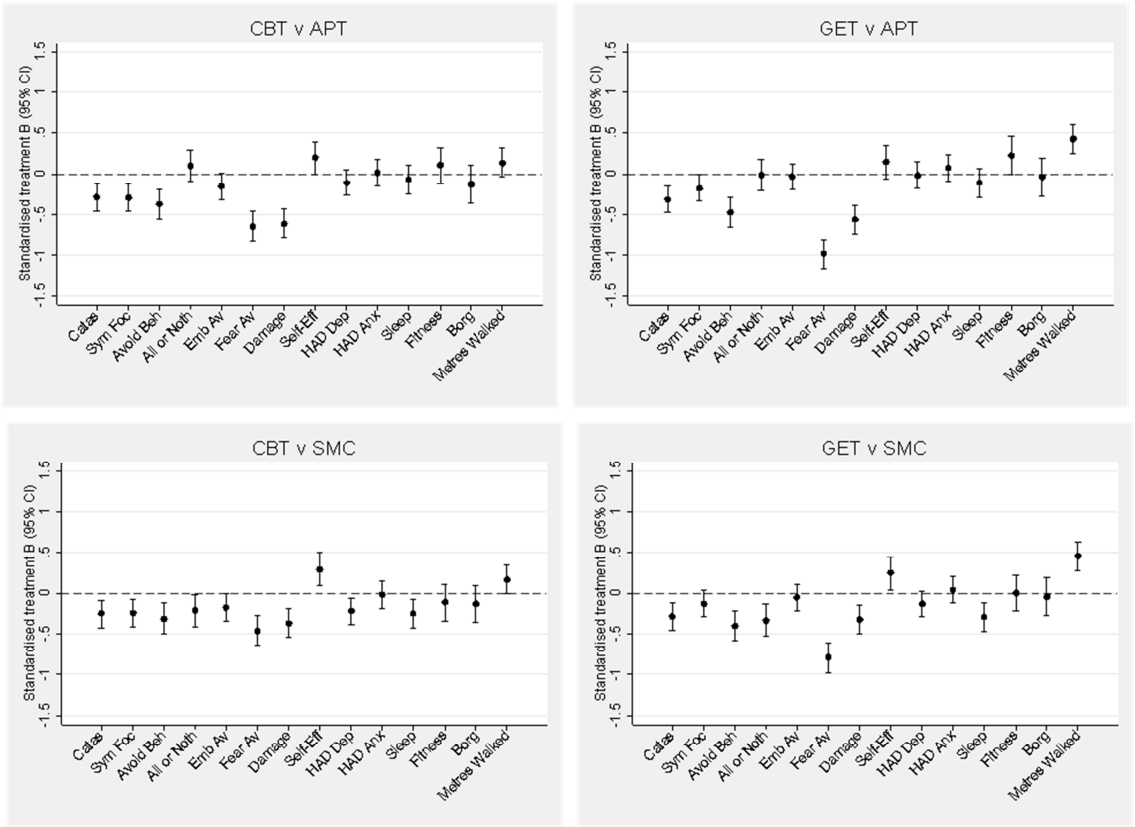
*For example, CBT versus APT
R = randomised treatment, M = mediator, Y = outcome, U = unmeasured confounders, *a* = *a* path (treatment to mediator), *b* = *b* path (mediator to outcome), *c'* = *c'* path (direct effect of treatment on outcome accounting for mediator), e2 = error term in mediator model, e3 = error term in outcome model

Figure 2. Unadjusted mean (95% CI) of putative mediator measures over time



APT= adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialist medical care. For mediation analysis, baseline measurements were used as covariates and 12 week measurements were used as mediators.

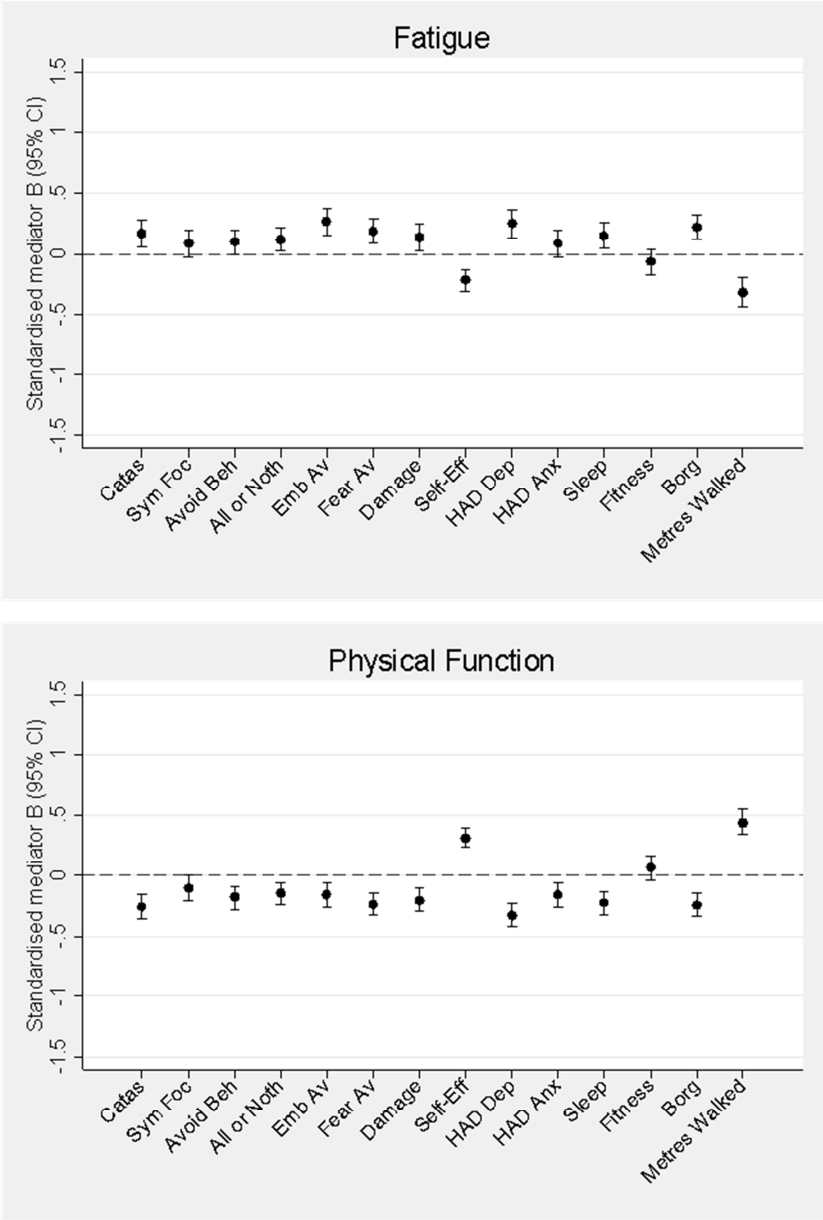
Figure 3. Standardised effects of treatments on putative mediators in SD units of the mediator*



*As well as treatment, models also included: centre, SCID depression status, London criteria for ME status, International criteria for CFS status, baseline measures of both outcome variables, baseline WSAS, SCID anxiety disorder status, age, gender, CFS group membership, receipt of benefits, benefits in dispute, physical illness attribution, fibromyalgia status, illness duration, Jenkins sleep score, employment status, body mass index and physical symptoms (PHQ-15) score.

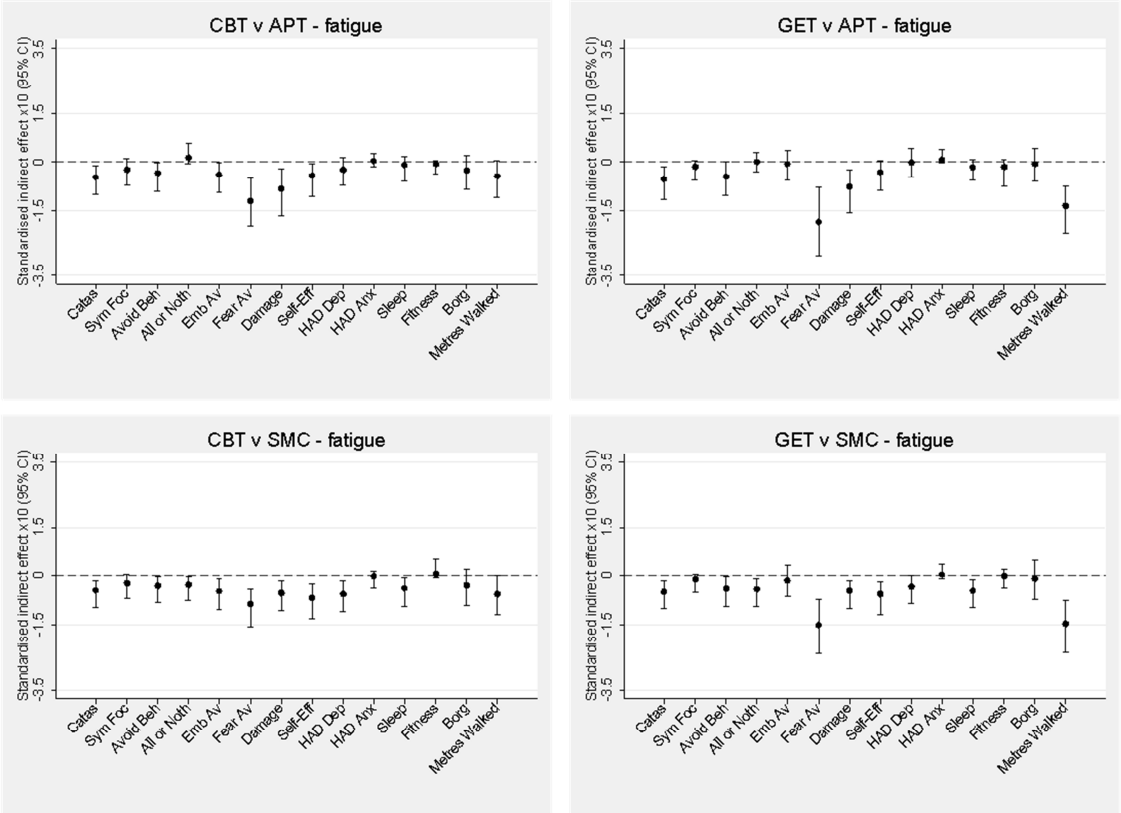
B = standardised beta parameter from model for mediator, CI = confidence interval, APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialist medical care, Catas = catastrophising, Sym Foc = symptom focusing, Avoid Beh = avoidance behaviour, All or Noth = all or nothing behaviour, Emb Av = embarrassment avoidance beliefs, Fear A = fear avoidance beliefs, Damage = damage beliefs, Self-Eff = self-efficacy, HAD = Hospital Anxiety and Depression Scale, Dep = HADS depression subscale, Anx = HADS anxiety subscale, Sleep = Jenkins Sleep Scale, Borg = adjusted Borg scale

Figure 4. Standardised effects of putative mediators on outcomes in SD units of the outcome *



*As well as treatment, models also included: centre, SCID depression status, London criteria for ME status, International criteria for CFS status, baseline measures of both outcome variables, baseline WSAS, SCID anxiety disorder status, age, gender, CFS group membership, receipt of benefits, benefits in dispute, physical illness attribution, fibromyalgia status, illness duration, Jenkins sleep score, employment status, body mass index and physical symptoms (PHQ-15) score.
B = standardised beta parameter from model for outcome, CI = confidence interval, APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialist medical care, Catas = catastrophising, Sym Foc = symptom focusing, Avoid Beh = avoidance behaviour, All or Noth = all or nothing behaviour, Emb Av = embarrassment avoidance beliefs, Fear Av = fear avoidance beliefs, Damage = damage beliefs, Self-Eff = self-efficacy, HAD = Hospital Anxiety and Depression Scale, dep = HADS depression subscale, anx = HADS anxiety subscale, Sleep = Jenkins Sleep Scale, Borg = adjusted Borg scale

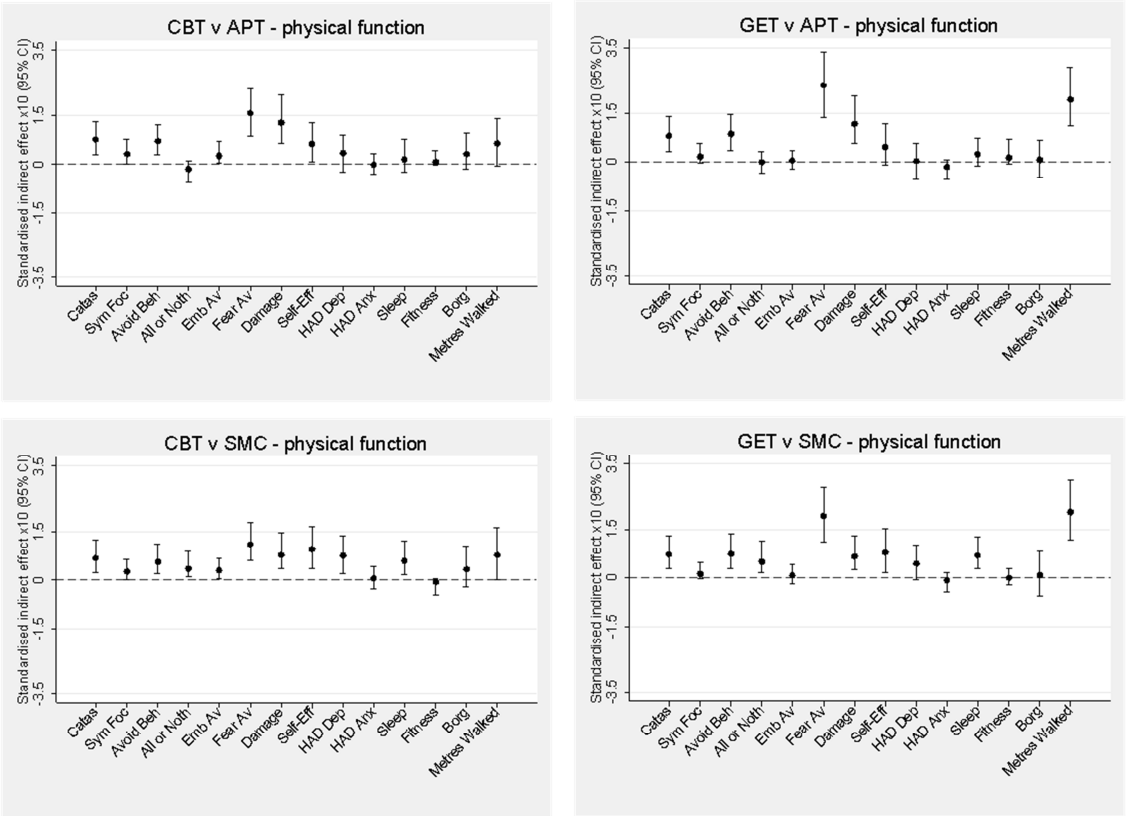
Figure 5. Standardised mediation effects in SD units of the outcome (times 10) of treatments on fatigue*



*As well as treatment, models also include: centre, SCID depression status, London criteria for ME status, International criteria for CFS status, baseline measures of both outcome variables, baseline WSAS, SCID anxiety disorder status, age, gender, CFS group membership, receipt of benefits, benefits in dispute, physical illness attribution, fibromyalgia status, illness duration, Jenkins sleep score, employment status, body mass index and physical symptoms (PHQ-15) score.

CI = confidence interval, APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialist medical care, Catas = catastrophising, Sym Foc = symptom focusing, Avoid Beh = avoidance behaviour, All or Noth = all or nothing behaviour, Emb Av = embarrassment avoidance beliefs, Fear Av = fear avoidance beliefs, Damage = damage beliefs, Self-Eff = self-efficacy, HAD = Hospital Anxiety and Depression Scale, dep = HADS depression subscale, anx = HADS anxiety subscale, Sleep = Jenkins Sleep Scale, Borg = adjusted Borg scale

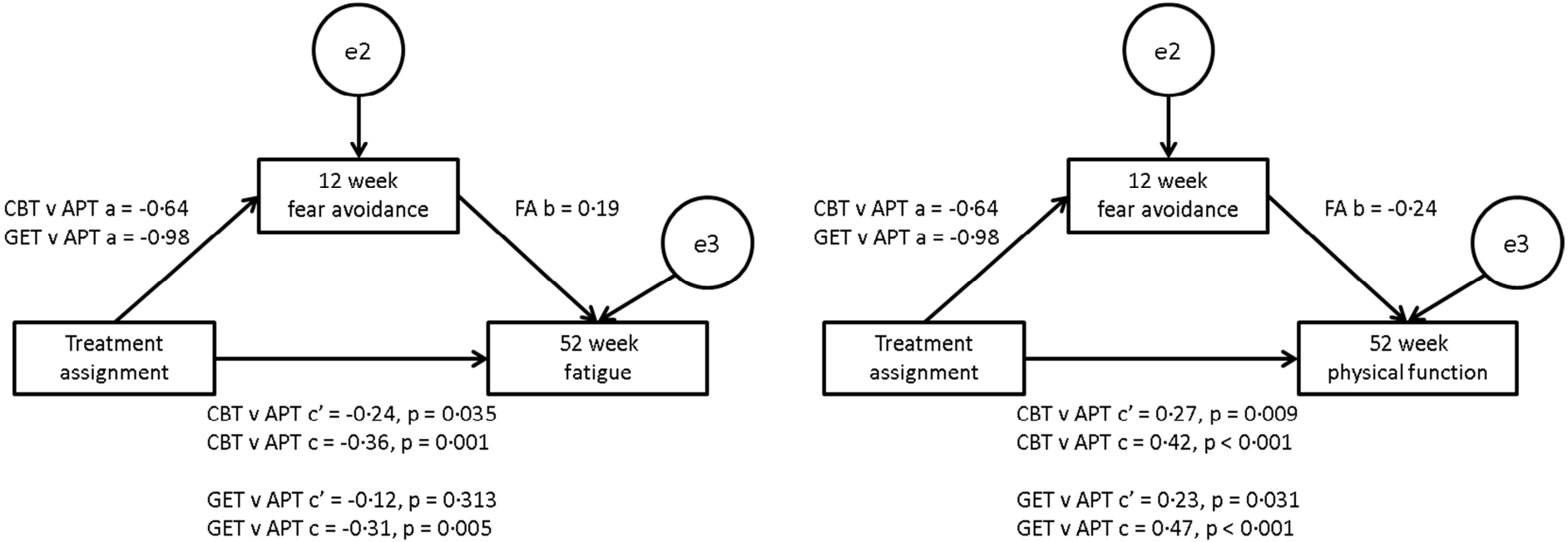
Figure 6. Standardised mediation effects in SD units of the outcome (times 10) of treatment on physical function*



*As well as treatment, models also include: centre, SCID depression status, London criteria for ME status, International criteria for CFS status, baseline measures of both outcome variables, baseline WSAS, SCID anxiety disorder status, age, gender, CFS group membership, receipt of benefits, benefits in dispute, physical illness attribution, fibromyalgia status, illness duration, Jenkins sleep score, employment status, body mass index and physical symptoms (PHQ-15) score.

CI = confidence interval, APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialist medical care, Catas = catastrophising, Sym Foc = symptom focusing, Avoid Beh = avoidance behaviour, All or Noth = all or nothing behaviour, Emb Av = embarrassment avoidance beliefs, Fear Av = fear avoidance beliefs, Damage = damage beliefs, Self-Eff = self-efficacy, HAD = Hospital Anxiety and Depression Scale, dep = HADS depression subscale, anx = HADS anxiety subscale, Sleep = Jenkins Sleep Scale, Borg = adjusted Borg scale

Figure 7. Standardised effects in mediation models through fear avoidance in SD units of the outcome



*As well as treatment, models also include: centre, SCID depression status, London criteria for ME status, International criteria for CFS status, baseline measures of both outcome variables, baseline WSAS, SCID anxiety disorder status, age, gender, CFS group membership, receipt of benefits, benefits in dispute, physical illness attribution, fibromyalgia status, illness duration, Jenkins sleep score, employment status, body mass index and physical symptoms (PHQ-15) score.
e2, e3 = model error terms, APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialist medical care, FA = fear avoidance beliefs